UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte DOSUK D. LEE and MARIA AIOLOVA

Appeal No. 2005-1927
Application No. 09/693,120

ON BRIEF

Before, ELLIS, ADAMS and GRIMES, Administrative Patent Judges.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal pursuant to 35 U.S.C. § 134 from the examiner's final rejection of claims 22-44, all the claims pending in the application. Claims 1-21 have been canceled.

As a preliminary matter, we note the appellants' statement on page 5 of the brief that the claims stand or fall together. Accordingly, we will consider the issues as they

apply to claim 22 which is representative of the subject matter on appeal. Said claim reads as follows:

> 22. An anticancer composition comprising a mixture of an anticancer agent and a calcium phosphate paste, said paste comprised of one or more nanocrystalline or poorly crystalline calcium phosphates and a physiologically acceptable fluid, the paste having an injectable or formable consistency at the time of administration and hardenable at the tumor site.

The references relied upon by the examiner are:

Gerhart et al. (Gerhart)	5,085,861	Feb. 4, 1992
Constantz et al. (Constanz)	5,782,971	Jul. 21, 1998

Yamamura et al. (Yamamura), "Antitumor Effects and Distribution of Adriamycin Incorporated into Hydroxyapatite Implants in a Cancer Rat Model Bearing Swarm Rat Chondrosarcoma," Jpn. J. Pharmacol, Vol. 66, pp. 433-438 (1994).

The claims stand rejected as follows:

I. Claims 22-44 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Yamamura in view of Gerhart and Constantz.

II. Claims 22-44 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 22-44 of co-pending Application No. 09/692,664.

We affirm.

Discussion

As indicated by claim 22, above, the present invention is directed to a pharmaceutical composition comprising a calcium phosphate paste which is said to be useful for the treatment of cancer. The specification discloses that prior investigators have constructed calcium phosphate cements comprising tetracalcium phosphate (TTCP) and dicalcium phosphate and the anti-cancer agent mercaptopurine (6-MP). Specification, p. 3, last para. "The addition of 6-MP was reported not to interfere with the setting properties of the cement; however, the drug release profile form [sic, from] the cement was not acceptable, presumably due to crystallization of the calcium phosphate cement with time."[1] Id., sentence bridging pp. 3-4. Thus, according to the specification "[t]he effectiveness of cement as a delivery system was not established, as only model in vitro release studies were reported." Id., p. 4, lines 3-4. The appellants' invention is said to be a mixture comprising an anticancer agent and a paste which "includes one or more nanocrystalline or poorly crystalline calcium phosphates and a physiologically acceptable fluid." Id., p. 5, lines 5-8. The mixture is said to have a formable consistency which can be injected and harden in vivo at a desired location, such as a tumor site. Id., lines 8-10. The present invention is also said to be an improved composition for the local treatment of cancer because it has excellent

[1] In the event of further prosecution of the application, the examiner may wish to consider the teachings in the specification with respect to the work of prior investigators. We point out that the claimed composition does not include a limitation with respect to a drug release profile.

biocompatibility, enables the controlled release of drugs, and is easy to administer. Id., p. 4, lines 20-22.

I.

The examiner relies on the combined teachings of Yamamura, Gerhart and Constantz to support his conclusion of obviousness. However, as discussed above, the claims stand or fall with representative claim 22. Since we limit our consideration of the issues as they apply to said claim, we find that Yamamura and Gerhart are sufficient to establish a prima facie case of obviousness. Thus, we need not reach the teachings of Constantz,[2] to affirm the rejection.

The examiner argues that Yamamura discloses "methods of implanting injectable doxorubicin [adriamycin] loaded [on] hydroxyapatite beads for treating [a bone] tumor." Answer, p. 4. The examiner acknowledges that Yamamura does not teach "a paste formulation." Id. However, to make up for this deficiency in the teachings of Yamamura, the examiner relies on Gerhart's disclosure [the abstract; col. 7, lines 30-46, and 60-67; col. 8, lines 1-20, Examples 2-3] of compositions in the form of injectable, moldable pastes (i) which comprise particulate calcium phosphate and a biologically-active agent; (ii) wherein the calcium phosphate has a particle size "within the instantly claimed nanocrystalline (see col. 7, lines 15-25)"; and (iii) which

[2] We find that Constantz demonstrates the state of the art with respect to the use of flowable paste-like compositions, comprising crystalline calcium phosphate and a therapeutic agent, as bone structural material.

solidify within ten (10) minutes after administration. Id. The examiner points out that Gerhart discloses (at col. 7, lines 45-67) that the calcium phosphate composition can be used in the treatment of bone cancer. Id. Thus, as we understand it, the examiner concludes that because Gerhart discloses injectable, moldable compositions comprising a particulate calcium phosphate and a pharmaceutically acceptable fluid which are readily administered for purposes of bone repair and replacement, and the use of said compositions for the administration of biologically active agents for the treatment of bone cancer, it would have been obvious to one of ordinary skill in the art to include an anticancer agent as taught by Yamamura in said compositions, in order to treat bone cancer. Id., p. 5.

In response, the appellants argue that Yamamura discloses implanting an adriamycin-loaded hydroxyapatite bead into the center of a chondrosarcoma tumor present in a rat. Brief, pp. 8-9. The appellants further argue that neither Yamamura nor Gerhart "teach or suggest a composition containing a calcium phosphate paste in combination with an anticancer agent," as set forth in representative claim 22. Id., p. 9. The appellants still further argue (Brief, p. 9) that

> Gerhart discloses a "bone cement . . . comprised of a particulate biocompatible calcium phosphate ceramic and particulate resorbable calcium salt dispersed in a cross-linked biodegradable polyester matrix . . . [that can be] used for bone/implant fixation, or as a filler or cement for bone repair" (see the Abstract). Gerhart also discloses that an antibiotic can be incorporated into the cross-linked biodegradable matrix (col. 4, lines 30-34, and col. 10, lines 48-54). Gerhart does not teach or suggest the incorporation of an anticancer agent into the bone cement.

In addition, the appellants contend that Gerhart only describes "a bone cement containing an antibiotic that is employed to fill bone cavities that remain following the excision of tumor-containing bone (see col. 13, lines 45-49)," but that the patent does not teach or suggest the inclusion of an anticancer agent in said cement. Brief, pp. 9-10. Thus, the appellants argue that "[t]he skilled artisan would not be motivated to combine Gerhart . . with Yamamura because . . . [neither] reference[] teaches or suggests the desirability of such a combination." Id., p. 11. We find these arguments unpersuasive.

It is well established that the examiner has the initial burden under § 103 to establish a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). To that end, it is the examiner's responsibility to show that some objective teaching or suggestion in the applied prior art, or knowledge generally available [in the art] would have led one of ordinary skill in the art to combine the references to arrive at the claimed invention. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

Contrary to the appellants' arguments, we find that Gerhart discloses a moldable calcium phosphate paste comprising at least one calcium phosphate which is hardenable at the desired location in the body. Although the appellants characterize Gerhart's composition as a "cement," the patent discloses that

> [s]urgical cements are well known in the art. Such cements are commonly used for implant fixation in the surgical replacement of joint and bone tissue with prosthetic appliances. At the time of surgery the cement, in a fluid or semi-fluid pre-cured form, is injected or otherwise applied between the bone and implant, flowing around the contours of the bone and implant and into the interstices of cancellous bone. Upon hardening (curing), the cement mechanically-interlocks the bone and implant [col. 1, lines 35-44].

With respect to Gerhart's "cement," in particular, we find that the patent discloses that it "comprises a particulate biocompatible calcium phosphate ceramic and a resorbable calcium salt dispersed in a cross-linked biodegradable polyester mix."[3] See, e.g., Gerhart, col. 4, lines 22-25 and lines 35-37. The preparation of the "cement" is said to involve "combining the polyester and . . . [a] cross-linking agent into a substantially homogeneous mixture, and adding the particulate calcium phosphate ceramic and calcium salt to form a moldable composite cement mass which hardens on curing, i.e., completion of the cross-linking reaction." Id., col. 5, lines 37-43. We further find that Gerhart discloses that "the rate of cross-linking (i.e. time for curing or hardening of the cement) can be adjusted by controlling the amount of DMT [dimethyltoluidene] added to the PPF/MMA [propylene glycol fumarate/methyl

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[3] With respect to the polyester component we find that Gerhart further discloses [col. 4, lines 53-61]:

> Representative carboxylic acids for formation of polyesters useful in this invention include Kreb's cycle intermediates such as citric, isocitric, cis-aconitic, alpha-ketoglutaric, succinic, malic, oxaloacetic and fumaric acid. Many of such carboxylic acids have additional functionalities which can allow cross-linking and therefore means for curing present cement formulation from a paste-like moldable mass to a hardened cement [emphasis added].

methacrylate] mixture." Id., col. 6, lines 23-26. We still further find that Gerhart discloses that

> [i]n the operating room, the surgeon mixes the powder and liquid (polymer plus cross-linker) phases to form a paste-like mass. In a preferred composition, the resulting surgical cement is comprised of approximately one third by weight of the liquid phase and approximately two thirds by weight of the particulate phase. . . . The cross-linking/curing process begins immediately at room temperature when the DMT is added. Alternatively all ingredients can be mixed together except for the benzoyl peroxide which is added when initiation of the curing process is desired. The cross-linking reaction can transform the bone cement from an injectable or moldable paste into a durable solid particulate composite within about 10 minutes [col. 7, lines 49-66][emphases added].

Gerhart discloses that the surgical cement can be "used for bone/implant fixation, or as a filler or cement for bone repair" [the abstract; see also, col. 1, lines 16-17; col. 3, lines 46-51; col. 4, lines 25-30]. Gerhart exemplifies the use of the invention "as a medication-bearing composition for the controlled delivery of medication in vivo as well as for use as a surgical cement for prosthetic applications," but states that "such descriptions are illustrative only and are not intended to be limiting in any way [col. 12, line 66- col. 13, line 3]." For example, according to Gerhart, said compositions can be employed for the repair of osteoporotic fractures, and "advantageously in the treatment of bone tumors." Gerhart, col. 13, lines 5-7 and lines 45-49.

In view of the foregoing, we find that the "cement" disclosed by Gerhart satisfies the claim limitations with respect to a calcium phosphate paste which comprises nanocrystalline or poorly crystalline calcium phosphates and a physiologically acceptable fluid, wherein the paste has an injectable or formable consistency at the

time of administration and hardenable at the tumor site (when said tumor site is in bone tissue).

We recognize that the present invention is directed to a composition which further comprises an anticancer agent. As indicated above, we find that Gerhart discloses that the moldable composition described therein can be used for the controlled-release delivery of biologically-active agents. See, e.g., Gerhart, the abstract; col. 1, lines 14-19; col. 8, lines 7-12. As a drug delivery system, Gerhart discloses [col. 8, lines 36-47] that the

> invention can be formulated and implanted, or injected, either before or after curing (the cross-linking reaction) is complete. The drug/cross-linked polymer/particulate composites are typically implanted surgically at a site in the body where high drug concentrations are desired. Thus, for example, in the treatment of osteomyelitis, antibiotic-containing composites can be molded to conform to naturally occurring bone defects or they can be inserted into cavities formed by the surgeon specifically for receiving the composition. Similarly, the composites can be implanted or injected into soft tissue for sustained drug release.

As pointed out by the examiner, Yamamura discloses that "adriamycin (ADR) is one of the anticancer drugs most widely used against malignant bone tumors." Yamamura, p. 433, col. 1., para. 2. In our view, given the teachings of Gerhart as to the use of the moldable calcium phosphate paste as a drug delivery system for the treatment of bone tumors, one of ordinary skill in the art would have been motivated to incorporate the well known and widely-used anti-cancer agent (ADR) taught by Yamamura into said paste.

Contrary to the appellants' arguments, we do not find that the teachings of Gerhart are limited to the incorporation of only antibiotics into the calcium phosphate paste. Rather, as discussed above, we find that Gerhart discloses that any biologically-active agent or drug can be combined with the paste to form "a medication-bearing composition for the controlled delivery of medication in vivo [col. 12, lines 66-68]." Moreover, even if we assume, arguendo, that the appellants are correct that Gerhart only suggests the addition of antibiotics to the calcium phosphate paste disclosed therein, we agree with the examiner that the ADR taught by Yamamura is an antibiotic.[4] Thus, regardless of whether the teachings of Gerhart are interpreted broadly or narrowly, we find that the combined teachings of Yamamura and Gerhart would have reasonably suggested the claimed composition to those having ordinary skill in the art.

We find the appellants' argument that one of ordinary skill in the art would not have had a "reasonable expectation of success for making and using" a composition as described in representative claim 22, to be unpersuasive.

First, we find that given the teachings of Gerhart with respect to the construction of compositions comprising a moldable calcium phosphate paste and biologically active agents (drugs and antibiotics) which hardens in vivo and the anticancer agent disclosed

[4] The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals,Twelfth Edition, Budavari et al., eds, Merck Research Laboratories, Whitehouse Station, NJ, pp. 581-582 (1996) discloses that doxorubicin (a.k.a. adriamycin) is an anthracycline antibiotic isolated from Streptomyces peucetius var. caesius.

by Yamamura, one of ordinary skill in the art would have a reasonable expectation of successfully making an anticancer composition as recited in representative claim 22.

Second, given the successful use of adriamycin (a.k.a. doxorubicin) in the treatment of bone cancer as taught by Yamamura, we find that such person would have reasonably expected that said composition would be successful in the treatment of bone cancer.

Finally, we note the appellants' arguments with respect to the nonobviousness of the kit recited in claims 42-44. Brief, pp. 14-15. However, as pointed out by the examiner (Answer, p. 14), these arguments are inconsistent with the appellants' statement (Brief, p. 5) that the claims stand or fall together. Attention is directed to 37 C.F.R. § 1.192(c)(7)(2004) which states, in relevant part, that

> For each ground of rejection which the appellant contests and which applies to a group of two or more claims, the Board shall select a single claim from the group and shall decide the appeal as to the ground of rejection on the basis of that claim alone unless a statement is included that the claims of the group do not stand or fall together . . .

Accordingly, since the appellants' arguments are not in compliance with the rule, they were not considered by the examiner. For the same reason, we also decline their consideration.

Accordingly, in view of the foregoing, Rejection I is affirmed.

II.

As indicated above, the claims are also provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 22-24 of co-pending Application No. 09/692,664. The appellants have merely requested that the rejection be held in abeyance. Brief, p. 5. Accordingly, since the rejection is not contested, we affirm.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

JOAN ELLIS
Administrative Patent Judge

DONALD E. ADAMS
Administrative Patent Judge

ERIC GRIMES
Administrative Patent Judge

) BOARD OF PATENT
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) INTERFERENCES

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